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Toxic metal exposure as a possible risk factor for COVID-19 and other respiratory infectious diseases



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ABSTRACT

Multiple medical, lifestyle, and environmental conditions, including smoking and particulate pollution, have been considered as risk factors for CoronaVirus Disease 2019 (COVID-19) susceptibility and severity. Taking into account the high level of toxic metals in both particulate matter (PM2.5) and tobacco smoke, the objective of this review is to discuss recent data on the role of heavy metal exposure in development of respiratory dysfunction, immunotoxicity, and severity of viral diseases in epidemiological and experimental studies, as to demonstrate the potential crossroads between heavy metal exposure and COVID-19 severity risk. The existing data demonstrate that As, Cd, Hg, and Pb exposure is associated with respiratory dysfunction and respiratory diseases (COPD, bronchitis). These observations corroborate laboratory findings on the role of heavy metal exposure in impaired mucociliary clearance, reduced barrier function, airway inflammation, oxidative stress, and apoptosis. The association between heavy metal exposure and severity of viral diseases, including influenza and respiratory syncytial virus has been also demonstrated. The latter may be considered a consequence of adverse effects of metal exposure on adaptive immunity. Therefore, reduction of toxic metal exposure may be considered as a potential tool for reducing susceptibility and severity of viral diseases affecting the respiratory system, including COVID-19.

1. Introduction

CoronaVirus Disease 2019 (COVID-19) is an infectious disease caused by coronavirus SARS-CoV-2 that first occurred in October and caused a massive outbreak in December 2019 (Frutos et al., 2020). During the last 10 months COVID-19 affected more than 30 million

people worldwide, and is considered as a cause of more than 950,000 deaths (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019>). The virus predominantly affects the respiratory system, causing COVID-19 pneumonia (Li et al., 2020a, 2020b, 2020c), although other systems are also involved especially in severe cases due to vascular dysfunction (Varga et al., 2020) and cytokine storm

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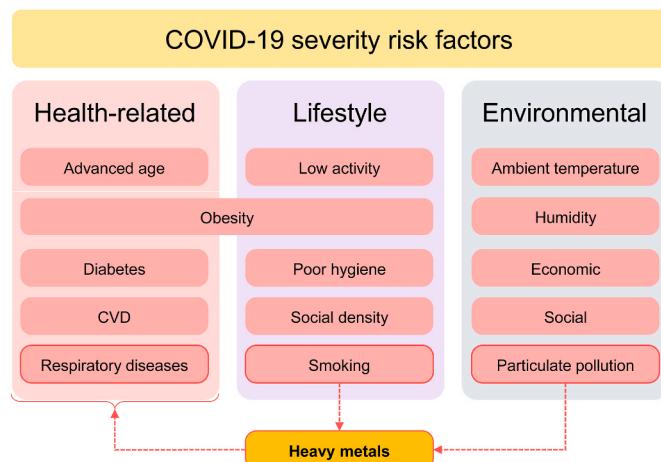


Fig. 1. The proposed role of heavy metals as a link between risk factors for COVID-19 severity. Both particulate (PM_{2.5}) pollution and smoking are associated with heavy metal exposure that at least partially mediate adverse effects of these factors on the respiratory system. In addition, heavy metal exposure was shown to be associated with higher incidence of obesity, diabetes, and cardiovascular diseases.

(Shimabukuro-Vornhagen et al., 2018) resulting in systemic inflammation (Yuki et al., 2020). These features are tightly linked to COVID-19-associated immune dysregulation (Li et al., 2020a, 2020b, 2020c) characterized by lymphopenia with a concomitant decline in T helper, T suppressor, and regulatory T cells, and leukocytosis, increased neutrophil-to-lymphocyte-ratio (Qin et al., 2020), as well as lymphocyte and NK-cell dysfunction (Vabret et al., 2020). The key symptoms include fever, cough, fatigue, expectoration, and dyspnea, as well as less common gastrointestinal symptoms including diarrhea, nausea and vomiting (Li et al., 2020a). Moreover, clinical course of the disease is highly variable, being characterized by high number of asymptomatic and mild cases, but frequently progressing to pneumonia, acute respiratory distress syndrome (ARDS) and organ dysfunction (Singhal, 2020). However, the particular causes of such clinical heterogeneity are unclear.

In parallel with the search for therapeutic approaches for the disease (Dong et al., 2020) and assessment of its safety (Javorac et al., 2020), estimation of the potential risk factors is also essential for management of the disease and reducing its risk (Zheng et al., 2020). Multiple medical, lifestyle, and environmental (Tsatsakis et al., 2020) conditions have been considered as risk factors for COVID-19 susceptibility and severity (Fig. 1). Given the key role of the respiratory system as a target for COVID-19, respiratory diseases including chronic obstructive pulmonary disease (COPD) (Lippi, Henry, 2020) were shown to be associated with higher disease severity. Obesity (Petrakis et al., 2020), diabetes, cardiovascular diseases (Zheng et al., 2020), and cancer (Dai et al., 2020) were also considered as risk factors for COVID-19 severity. Advanced age is known to be one of the leading factors associated with severity of the disease due to impaired immune response (Wu et al., 2020a). A recent study originating from the UK has demonstrated that lifestyle factors may account up to 51% variability in COVID-19 severity with physical inactivity, obesity, and smoking being the leading ones (Hamer et al., 2020). SARS-CoV-2 is the causal factor contributing to the COVID-19 pandemic; still environmental factors such as humidity, UV radiation and ambient temperature were shown to affect disease susceptibility and SARS-CoV-2 transmissibility (Ma et al., 2020). Environmental gas and particulate pollution were also shown to affect epidemiological parameters of COVID-19 infection (Yongjian et al., 2020). In view of the role of toxic metals as effector agents in tobacco smoke and particulate pollution toxicity, as well as their respiratory, immunotoxic, and proinflammatory effects, we propose that toxic metal

exposure may be also considered as a potential risk factor for COVID-19 severity.

Therefore, the objective of the study was to discuss recent data on the role of toxic metal exposure in development of respiratory dysfunction, immunotoxicity, as well as interference of metal toxicity with viral diseases in epidemiological and experimental studies in order to demonstrate the potential crossroads between heavy metal exposure and COVID-19 severity risk. In order to address the objective we have performed a systematic search in the PubMed database using the MeSH terms cadmium, mercury, lead, arsenic, lungs, respiratory function, inflammation, mucociliary clearance; bronchitis, viral diseases, antiviral immunity, immunotoxicity up through August 20, 2020.

1.1. Metal-related risk factors for severe COVID-19

Environmental pollution has been considered to be one of the risk factors for COVID-19 severity and mortality due to impaired respiratory functions, chronic inflammation, and reduced resistance to infections (Conticini et al., 2020; Qu et al., 2020), being supported by indirect data from Northern Italy and China (Martelletti, Martelletti, 2020). Particularly, an increase in PM_{2.5}, PM₁₀, NO₂ and O₃ concentrations in 120 cities in China has been associated with newly confirmed COVID-19 cases (Zhu et al., 2020). In addition, it has been demonstrated that every 1 µg/m³ increase in PM_{2.5} level results in an 8% increase in COVID-19 mortality rate (Wu et al., 2020b). However, despite the presence of rather convincing data on the role of environmental pollution as a risk factor for COVID-19 susceptibility, these conclusions should be viewed with caution due to lack of qualitative and quantitative analysis of particulate matter (Contini, Costabile, 2020). It has been also proposed that heavy metals may significantly mediate health hazards of particulate matter (Chen, Lippmann, 2009).

Another potential external factor associated with COVID-19 severity is smoking, although the existing data are highly contradictory. A recent analysis revealed a nearly twofold higher risk of severe COVID-19 (odds ratio (OR) = 1.98; 95% confidence interval (95%CI): 1.29–3.05) (Zhao et al., 2020). However, sensitivity analysis demonstrated that the study by Guan et al. (2020) originating from Wuhan was considered as the main source of heterogeneity, and its exclusion resulted in insignificant association between smoking and COVID-19 severity. Other studies also met with contradictions, indicating both lack of an association (Lippi, Henry, 2020) and a direct association between smoking and COVID-19 severity (Vardavas, Nikitara, 2020). Finally, a systematic review and meta-analysis dated from June 2020 has been demonstrated that current smokers have higher odds for adverse outcome of COVID-19 than non-current smokers, but lower risk in comparison to former smokers (Farsalinos et al., 2020a,b).

Despite significant contradiction in epidemiological data, smoking induced up-regulation of ACE2 receptor (Brake et al., 2020) in addition to lung inflammation, impaired barrier functions, mucus over-production, and mucociliary clearance (Berlin et al., 2020) that could be mechanistically linked to higher risk of COVID-19. Hazardous effects of tobacco smoke could be attributed to the presence of more than 5000 chemicals, with heavy metals such as cadmium and lead being among the 98 most toxic agents (Talhout et al., 2011).

Taken into account a high level of toxic metals in both particulate matter and tobacco smoke, it is reasonable to propose that metal toxicity may in part underlie the association between PM exposure and COVID-19 severity, although this hypothesis has yet to be confirmed.

1.2. Cadmium

1.2.1. Respiratory dysfunction and diseases

Cadmium (Cd) was shown to underlie a significant part of adverse effects of tobacco smoke exposure through induction of oxidative stress and impaired macrophage functions (Sarigiannis and Salifoglou, 2016; Ganguly et al., 2018). Particularly, it has been demonstrated that

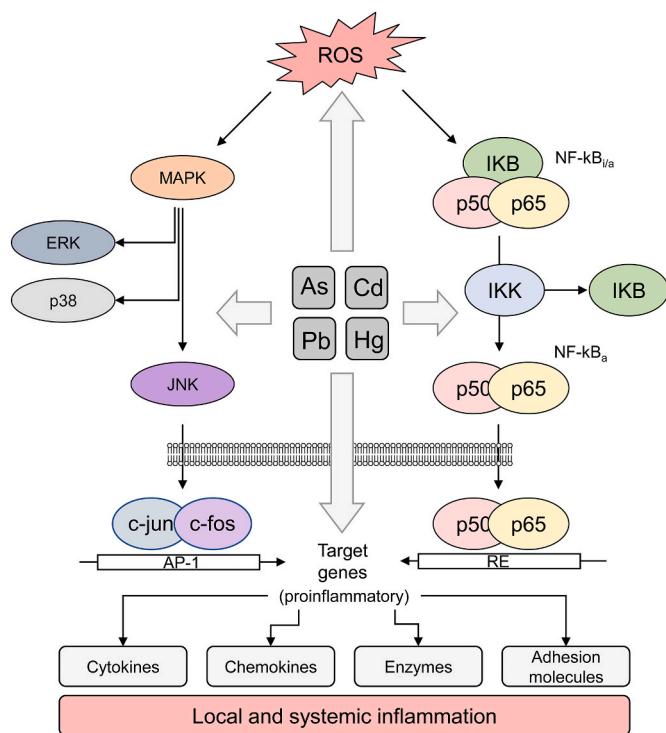


Fig. 2. A simplified scheme depicting proinflammatory mechanisms of heavy metals. Briefly, heavy metal exposure results in increased ROS production and oxidative stress that latter may underlie heavy metal-induced activation of proinflammatory pathways NF-κB and MAPK with subsequent expression of target proinflammatory genes including cytokines, chemokines, enzymes, and adhesion molecules (Metryka et al., 2018; Pollard et al., 2019; Hosseini-Khanzadeh et al., 2020; Hu et al., 2020).

urinary Cd levels were associated with lower forced expiratory volume (FEV1) values in current and former smokers, but not in never smokers (Mannino et al., 2004). Cd and lead (Pb) co-exposure resulted in reduced FEV1 and FVC in children living in e-waste recycling area (Zeng et al., 2017). Similar associations between blood Cd and forced vital capacity (FVC), FEV1, FEV1/FVC, peak expiratory force (PEF) were shown in welders (Cetinteppe et al., 2019; Torén et al., 2019). Even upon low Cd body burden in exposed workers, urinary Cd levels were associated with higher prevalence of subjective respiratory symptoms despite the lack of

significant changes in lung function (Li et al., 2020b).

Several studies have demonstrated the association between Cd exposure markers and respiratory diseases. Cd levels were found to be increased in cell-free bronchoalveolar lavage (BAL) fluid in smokers as compared to non-smokers in a cohort of patients with chronic obstructive pulmonary disease (Sundblad et al., 2016). These findings corroborate observations on higher blood Cd levels in male COPD patients (Oh et al., 2014). It is also noteworthy that in a case-control study conducted in Wuhan, China, urinary Cd levels were inversely associated with FEV1 values (Huang et al., 2016). Cd exposure was also associated with higher risk of wheezing in current smokers in the NHANES 2007–2012 (Yang et al., 2019a). In agreement, hair Cd levels in children were also associated with the number of wheezing episodes even after adjustment for environmental tobacco smoke (Razi et al., 2012).

1.2.2. Mechanisms of respiratory toxicity

Cd exposure possesses both proinflammatory effects in lung tissue (Fig. 2), resulting in higher susceptibility to infectious diseases (Kulas et al., 2019). The mechanisms of Cd toxicity in lung cells may also involve endoplasmic reticulum (ER) stress (Kim et al., 2017) and up-regulation of apoptosis (Heo et al., 2017a, 2017b). Particularly, Cd exposure resulted in activation of proapoptotic signals (Bax, caspase 8) and repression of antiapoptotic Bcl-2 signaling in A549 lung cells (Kiran Kumar et al., 2016). Apoptosis is also known to be involved in the regulation of Cd-induced autophagy in A549 cells (Li et al., 2019).

Cd exposure was shown to induce peribronchiolar fibrosis and lung remodeling due to stimulation of vimentin phosphorylation (Li et al., 2017a, 2017b). In addition, SMAD-dependent myofibroblast differentiation from lung fibroblast may also underlie Cd-associated pulmonary fibrosis (Hu et al., 2017). Correspondingly, low-dose Cd exposure aggravated polyhexamethylene guanidine-induced lung fibrosis through up-regulation of inflammatory and fibrotic mediators (Kim et al., 2018). Cd exposure in the form of Cd nanoparticles was shown to induce citrullination of proteins (cytokeratins I and II) in lung epithelial cells (Hutchinson et al., 2018).

Cd exposure also results in impaired mucociliary clearance and aberrant mucin production associated with oxidative stress, inflammation, and activation of matrix metalloproteinases in a human airway tissue *in vitro* model (Xiong et al., 2019). In addition, CdCl₂ is also capable of decreasing barrier function of bronchial epithelial cells through altered expression of tight junction proteins zonula occludens-1 (ZO-1) and occluding (Cao et al., 2015).

One of the potential mechanisms of lung damage in response to Cd

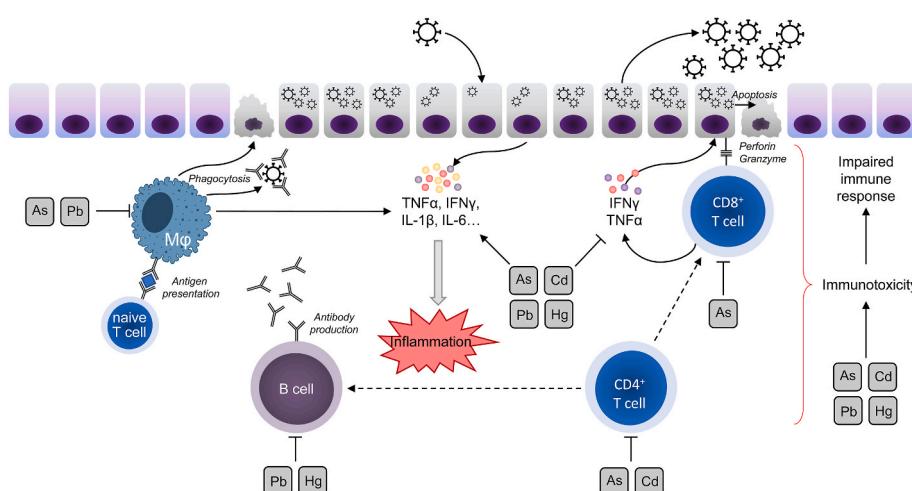


Fig. 3. The proposed impact of heavy metals on antiviral immunity. As, Cd, Hg, and Pb were shown to be toxic for both T and B lymphocytes, as well as macrophages, affecting its proliferation and further functioning. Taken together with the negative impact on IFN γ production and proinflammatory activity, heavy metals may significantly contribute to excessive inflammatory and impaired immune response.

exposure may include antagonistic relationships between the latter and zinc (Zn) ions (Xu et al., 2017; Knoell et al., 2020) that is involved in respiratory protection (Skalny et al., 2020).

1.2.3. Viral diseases, antiviral immunity, and immunotoxicity

In an experimental study, oral Cd pretreatment was accompanied by significantly increased titers of respiratory syncytial virus (RSV) in lung tissues and severe lung damage due to aggravation of inflammation, oxidative stress, and mitochondrial dysfunction (Go et al., 2018). Correspondingly, Cd exposure potentiated inflammatory lung damage in a murine model of H1N1 infection (Chandler et al., 2019). In addition, Cd exposure promoted influenza virus replication in MCDK cells in a dose-dependent manner (Checconi et al., 2013). Several epidemiological (Krueger, Wade, 2016) and laboratory (Seth et al., 2003) studies also indicated the association between Cd exposure and non-airborne viral diseases, that may be generally attributable to immunotoxic effect of Cd and its negative impact on antiviral immunity (Fig. 3).

Cd toxicity is associated with altered hematopoietic stem and progenitor cells differentiation causing a shift to myelopoiesis from lymphopoiesis (Zhang et al., 2016). In addition, Cd affects T cell subsets characterized by reduction of T-helper ($CD4^+$) cells and induction of cytotoxic T cells ($CD8^+$), being indicative of metal immunotoxicity, and resulting in down-regulation of interferon- γ (IFN- γ) and interleukin-2 (IL-2) production (Pathak, Khandelwal, 2008). Developmental Cd exposure was shown to affect immune system maturation through alteration of DN1 and DN2 thymocyte ratio, also resulting in reduced natural killer (NK)-cell and granulocyte content in spleen accompanied by increased $CD4^+$ and $CD8^+$ T cells, as well as $CD45R/B220^+$ B cells count (Holásková et al., 2012). More recently, a study conducted in male Sprague-Dawley rats demonstrated that subchronic exposure to Cd (32 ppm cadmium chloride in drinking water for 10 weeks) led to a slight increase in the relative weight of the spleen and in the regulatory T cells number. Cd-exposed animals also showed a significant increase in the production of IFN- γ and IL-10, suggesting an impact on immune cell function and cellularity, which may stimulate inflammatory responses (Turley et al., 2019). Generally, these findings are indirectly in agreement with the observation on the inverse association between Cd exposure and T lymphocyte (Zeng et al., 2020) and memory T cell levels in children (Nygaard et al., 2017).

The immunotoxic effect of Cd exposure is also associated with development of aberrant inflammatory response due to altered cytokine expression profile (Hossein-Khannazer et al., 2020). Earlier data have demonstrated that adult female zebrafish exposed to 1 mg L⁻¹ Cd for 24 or 96 h led to an increase in the levels of tumor necrosis factor- α (TNF- α) in the brain, liver and ovary, as well as increase in mRNA levels of nuclear factor erythroid 2-related factor 2 (Nrf2) and nuclear factor- κ B (NF- κ B) in the liver and ovary in the first evaluation time (Zheng et al., 2016). On the other hand, zebrafish embryos exposed for 15 weeks to 5 μ g/L Cd presented a decrease of nitric oxide (NO) and iNOS levels in the liver and spleen, accompanied by decreased transcriptional levels of IL-6, IL-10, IL-1 β and TNF- α in liver. These findings indicate an immunosuppressive activity of Cd that was followed by a compensatory effect observed due to an increase in the mRNA levels of these cytokines in the spleen (Guo et al., 2017).

In vitro, exposure to various concentrations of Cd caused decreased viability of RAW 264.7 cell line, murine macrophage-derived cell. Increase in the production of reactive oxygen and nitrogen species was observed in response to activating stimulus by *Salmonella enterica* Serovar Enteritidis via pattern-recognition receptors (PRRs). When exposed to CdCl₂, proinflammatory cytokines IL-12 and chemokine (C-X-C motif) ligand 1 (CXCL1) were highly upregulated whereas IL-6 and IL-10 were suppressed, indicating an important effect of cadmium on the macrophage functions modulation in innate immune response to infection (Riemschneider et al., 2015). Cd exposure may also sustain systemic inflammatory reaction through modulation of gut microbiota and subsequent increase in LPS levels (Tinkov et al., 2018b).

1.3. Mercury

1.3.1. Respiratory dysfunction and diseases

Although respiratory dysfunction is known to be the characteristic feature of acute mercury (Hg) vapor inhalation (Smiechowicz et al., 2017), data on the relationship between environmental Hg pollution and pulmonary function are rather insufficient. Previous studies revealed a significant inverse association between hair Hg and respiratory function in subjects from artisanal and small-scale gold mining areas (Pateda et al., 2018). High serum Hg levels (third tertile) were associated with increased odds of obstructive lung disease (OR = 3.62; 95%CI: 1.29–10.18) in a dusty area (Heo et al., 2017a, 2017b). The results of a follow-up analysis involving 4350 Korean children demonstrated that blood Hg is associated with higher odds of asthma and bronchi hyperresponsiveness (Kim et al., 2015). However, further data show contradictory results, underlining the importance of investigation of the association between prenatal and lifetime Hg exposure and asthma (Heinrich et al., 2017). Serum mercury as well as lead levels were found to be higher in children with recurrent wheezing (Razi et al., 2011). Blood Hg levels were also associated with increased exhaled nitric oxide levels, being considered as a marker of airway inflammation (Min, Min, 2013). It is also notable that high maternal toenail Hg content was associated with increased risk of lower respiratory infections, but not upper respiratory tract infections in infants (Emeny et al., 2019).

1.3.2. Mechanisms of respiratory toxicity

Both methylmercury (CH₃Hg) (Yu et al., 2015) and HgCl₂ (Park, Park, 2007) were shown to be cytotoxic for A549 cells through induction of oxidative stress and apoptosis. The latter may occur due to Hg-induced modulation of Bax, p53, and Bcl 2 expression (Ali et al., 2018). Similar effect was observed in alveolar type II epithelial cell exposed to mercury (Lu et al., 2010). Correspondingly, both Hg and Cd exposure were shown to induce oxidative stress accompanied by heat shock protein 70 (Hsp 70) expression, although Cd was relatively more toxic as compared to Hg (Han et al., 2007). ER stress may be also considered as the potential mechanism of lung toxicity of Hg (Jagannathan et al., 2017). It is also notable that inhalation of elementary mercury vapor significantly up-regulated proinflammatory cytokine expression in lung tissue (Liu et al., 2003).

Although direct data on the impact of Hg on airway epithelium permeability are insufficient, it has been demonstrated that Hg exposure affects expression of tight junction proteins in colonic epithelial cells (Vazquez et al., 2014).

Morphological analysis demonstrated that Hg exposure may induce inflammatory response characterized by inflammatory cells infiltration and altered extracellular matrix (Naidoo et al., 2019) through proinflammatory effect of the metal (Fig. 2).

1.3.3. Viral diseases, antiviral immunity, and immunotoxicity

Several epidemiological and experimental studies have demonstrated the association between Hg exposure and airborne viral infections. The association between mercury exposure and measles antibodies was found to be significant only in children with low folate and high methylmalonic acid (MMA) values, whereas in other children the relationship was found to be inverse (Gallagher et al., 2011). Similarly, associations between Hg and rubeola antibody levels were affected by folate, MMA, and homocysteine levels (Gallagher et al., 2013).

Experimental studies have clearly demonstrated that Hg exposure may modulate manifestation of airborne viral infections. In particular, pretreatment with inorganic Hg significantly aggravated coxsackievirus B3 (CVB3) infection-induced myocarditis characterized by severe macrophage infiltration and proinflammatory cytokine overproduction, whereas posttreatment did not possess similar effect in mice (Nyland et al., 2012; Penta et al., 2015b). It is also notable that coxsackievirus B3 (CB3) infection in mice is accompanied by a twofold increase in brain Hg content, whereas Se levels were found to be elevated only by 36%

(Ilbäck et al., 2005). Taken together with a later observed decrease in intestinal, serum, and hepatic Hg levels (Ilbäck et al., 2008), these findings are indicative of redistribution of Hg into brain providing an additional link between viral diseases and neurotoxicity. The observations on positive association between body Hg burden and parenterally-transmitted HIV infection (Emokpae, Mbonu, 2018) also support indirectly the impact of Hg on antiviral immunity.

In view of the role of bats as carriers for SARS-CoV-2 (Docea et al., 2020), it is also noteworthy that high Hg levels in bats are associated with impaired immunity and higher susceptibility to infectious agents (Becker et al., 2017). It is notable that the role of environmental, including heavy metals, and/or pollution may play a significant role in increased susceptibility of host organisms to viral zoonotic infections was also earlier proposed by Rotshild (2015).

The observed interference between Hg toxicity and viral infections may be mediated by immunotoxic effect of the metal (Gardner, Nyland, 2016) (Fig. 3). Particularly, it has been demonstrated that ethylmercury (thiomersal) and methylmercury, but not HgCl₂ possessed cytotoxic effect in a human T cell line (Jurkat) (Guzzi et al., 2012).

Notably, Weigand et al. (2015) showed that exposure of T and B cell lines (EL4 T cells and WEHI-231 B cells) to low doses of mercury (II) chloride (HgCl₂) during 12 or 96 h induced, in the absence of antigenic stimulation, increased levels of signaling molecules, such as ERK1/2, PKC α and p38MAPK, indicating inappropriate activation of these cells. MeHg exposure in Steller sea lion was shown to alter T and B cell proliferation due to aberrant expression of regulatory cytokines including INF- γ , IL-6, IL-10, and TNF- α (Levin et al., 2020). Increased susceptibility to fungal infections was also associated with reduced number of splenic CD3⁺CD4⁺ lymphocytes, as well as Th1 and Th17 cells (Batis-ta-Duharte et al., 2018).

In utero exposure of BALB/c mice to HgCl₂ by subcutaneous injection was able to induce a significant upregulation of arginase, IFN- γ , STAT1, vitronectin, and TNF Superfamily Member 1 (TNFSF18) in male offspring. These changes, being more pronounced in males, may modulate the baseline immune response and thus reflect risks in adulthood health (Penta et al., 2015a). At the same time, another study demonstrated that MeHg exposure may result in suppression of interferon- γ (IFN- γ) production in peripheral blood mononuclear cells (De Vos et al., 2007). In a more recent study, male C57BL/6 mice exposed subcutaneously to 25 mg/kg/day of methylmercury chloride presented, after seven days, increased expression of TNF- α -related genes in samples of different tissues, including liver, kidney and brain. The same study which included mouse neural cell line (C17.2 cells) also clarified that NF- κ B may participate as a transcription factor in the TNF- α induction (Iwai-Shimada et al., 2016), being indicative of the impact of Hg exposure on systemic inflammation (Maqbool et al., 2017). In addition, Hg-induced inflammation is tightly interrelated with autoimmunity (Pollard et al., 2019) that may also impair physiological immune and inflammatory reactions.

1.4. Lead

1.4.1. Respiratory dysfunction and diseases

Several studies have demonstrated an inverse association between environmental lead exposure levels and impaired respiratory function. Specifically, blood lead Pb levels were shown in Polish schoolchildren to have a negative effect on lung vital capacity (VC) and FVC (Little et al., 2017). Living in an e-waste emission area resulted in a significant increase in blood Pb levels that were inversely associated with FEV1 in children (Zeng et al., 2017). It has been also demonstrated that Pb exposure assessed by urinary metal levels is associated with reduced lung function (FEV1) especially as a result of interaction between Pb exposure and antioxidant (NQO1, NAD(P)H quinone dehydrogenase) gene polymorphisms (Wei et al., 2020). Moreover, of all heavy metals studied (Hg, Cd, Pb) only blood Pb levels were inversely and adversely associated with pulmonary function assessed by FEV1 and FVC (Pan

et al., 2020).

Pb exposure is known to play a causal role in respiratory disease (Boskabady et al., 2018). Heavy metals including lead were found to be higher in patients with COPD, being interrelated with pulmonary dysfunction and antioxidant activity (Gogoi et al., 2019). Correspondingly, soil and water lead distribution was shown to be associated with patterns of respiratory disease burden in Iran (Ghias, Mohammadzadeh, 2016).

1.4.2. Mechanisms of respiratory toxicity

Lead was found to be one of the metals primarily accounting for PM toxicity in A549 lung cells (Yuan et al., 2019) due to multiple mechanisms. Briefly, intratracheal instillation of Pb nanoparticles was also shown to induce oxidative stress (Lu et al., 2015) and inflammation resulting in lung damage (Li et al., 2013). It is also notable that lung inflammation and fibrosis in Pb-exposed rats were accompanied by a dose-dependent decrease of lung magnesium (Mg) content (Attafi et al., 2018).

Both oxidative stress and inflammation were linked to apoptotic death of lung cells in a model of Pb-induced lung injury in rats, whereas these effects were ameliorated by AMPK/Nrf2 activation (Lu et al., 2018). In particular, Pb exposure induced apoptosis in A549 cells through up-regulation of p53, bax, caspase 3 and 9 and down-regulation of bcl2 mRNA expression (Ahamed et al., 2019). Pb-induced mitochondrial dysfunction may also underlie proapoptotic signaling in the exposed lung cells (Alarifi et al., 2017). Activation of NF- κ B and aryl hydrocarbon receptor (AhR) pathways has been considered as the potential mechanism underlying Pb-induced inflammation and toxicity in A549 lung cells (Attafi et al., 2020) (Fig. 2).

Pb-induced lung toxicity is responsible for lung remodeling. In particular, detailed studies by Kaczyńska et al. (2011, 2013) demonstrated that 5-week lead exposure resulted in infiltration (Kaczyńska et al., 2011), alveolar fibrosis, emphysema, and degeneration of type II pneumocytes (Kaczyńska et al., 2013).

1.4.3. Viral diseases, antiviral immunity and immunotoxicity

Several studies demonstrated a relationship between Pb exposure and susceptibility to viral infections, corroborating its role in suppression of antiviral immunity (Rashed, 2011; Emokpae, Mbonu, 2018; Sahin et al., 2019), although no association between Pb and airborne viral infections exists.

Pb is a known toxicant to many organs, however, its mechanisms of action on the immune system are not well-established (Fenga et al., 2017) (Fig. 3). Briefly, lead exposure was shown to inhibit lymphocyte proliferation along with impaired IL-2 and calmodulin production (Li et al., 2012). In addition, Pb exposure was shown to alter Th1/Th2 ratio in chicken blood lymphocytes (Fu et al., 2019). Lead inhalation in sensitized guinea pigs was shown to alter IFN- γ /IL-4 ratio, being indicative of reduction in Th1/Th2 balance (Boskabady et al., 2012). Pb²⁺ was also shown to be toxic to both B-lymphocytes and especially macrophages, also resulting in reduced IFN- γ production and causing aberrant immune response to viral and bacterial pathogens (Han et al., 2020). These findings corroborate the observed inverse correlation between blood lead levels and T cell count in Pb-exposed subjects (Mishra et al., 2010). However, Pb exposure due to habitation in e-waste area is directly associated with increased number of memory T cells (Cao et al., 2018). Exposure of chicken neutrophils to Pb²⁺ resulted in a significant increase in IL-1 β , 1R, 4, 8, 10, and 12 β levels, whereas IL-2 and IFN- γ were down-regulated (Xing et al., 2018).

Early-life Pb exposure was shown to inhibit stimulated thymocyte and splenocyte proliferation also resulting in a dose-dependent decrease in IL-2, IFN- γ , IL-4, IL-10, and TNF- α secretion (Ajouaoi et al., 2019). In addition, Pb²⁺-induced thymocyte apoptosis is considered as the potential mechanism of lead immunotoxicity (Nishizaki et al., 2003).

Dvorožnáková et al. (2016) evaluated the effects of Hg, Cd and Pb in the immune response using a parasite-infection model. As regards Pb,

BALB/c male mice exposed during 35 days and subsequently infected with *Ascaris suum* on the 21st day presented increase in the levels of IL-5 and IL-10 cytokine production, but TNF- α and IFN- γ production was suppressed. In this study, continuous intoxication with Pb caused susceptibility to the parasite infection.

1.5. Arsenic

1.5.1. Respiratory dysfunction and diseases

Arsenic (As) exposure is known to cause a wide spectrum of malignant and non-malignant respiratory diseases (Ramsey, 2015). However, even subtoxic doses of arsenic may significantly affect respiratory functions. Particularly, a recent meta-analysis demonstrated that arsenic exposure is associated with restrictive impairments in lung function including reductions in forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) (Sanchez et al., 2018). Another study has demonstrated that As-associated FVC reduction is observed on males (Khan et al., 2020). In addition, overweight and obesity were shown to aggravate As-induced lung dysfunction (Nardone et al., 2017). Moreover, impaired lung function in As-exposed children (Ahmed et al., 2017) and adults (Wang et al., 2020; Shih et al., 2020) was also associated with lung inflammation. Spirometric abnormalities in As-exposed children were also associated with higher matrix metalloproteinase-9 (MMP-9) level in sputum (Olivas-Calderón et al., 2015).

Early-life and lifetime As exposure were shown to be associated with reduced respiratory function, as well as higher incidence of respiratory diseases including chronic cough and chronic bronchitis (Steinmaus et al., 2016), even after adjustment for smoking status (Powers et al., 2018). As exposure was also associated with reversible lung obstruction (Siddique et al., 2020).

Doubling of maternal urinary As levels was associated with increased incidence of infections, respiratory symptoms, diarrhea, and fever resulting in a doctor visit or medication use in first-year children (Farzan et al., 2016), with the strongest relationship observed for lower respiratory tract infections (Farzan et al., 2013). Specifically, increased urinary As concentrations ($\geq 6 \mu\text{g/L}$) were associated with a more than twofold increase in pneumonia risk (odds ratio (OR) 95% confidence interval (CI) = 1.88 (1.01, 3.53)) in Bangladeshi children (George et al., 2015).

1.5.2. Mechanisms of respiratory toxicity

As exposure has been shown to increase airway inflammation, reactivity, and remodeling characterized by peribronchial thickening that may be related to NLRP3 inflammasome activation (Surolia et al., 2020). As-induced lung damage was also shown to be associated with apoptotic cell death due to oxidative and endoplasmic reticulum stress (Gu et al., 2016), as well as mitochondrial dysfunction (Mahalanobish et al., 2019). Both inflammatory and prooxidant effects of As exposure in lungs may be related to As-induced up-regulation of NF- κ B and MAPK activity, as well as alteration of Nrf2 signaling, respectively (Li et al., 2017a, 2017b) (Fig. 2). Particularly, As is capable of up-regulation of IKK α/β and NF- κ B p65/50 mRNA and protein expression in parallel with a decrease in I κ B α levels in lungs (Hu et al., 2019). It is noteworthy that low-dose As exposure was shown to increase autophagy and inflammation in murine lungs, whereas high-dose As aggravated inflammatory response with weak autophagy activation (Zhao et al., 2019).

Prenatal As exposure was shown to impair expression of genes involved in lung morphogenesis (Sox 2), mucus production (Clca3, Muc5b), and ciliary function (Ttc21a) (Zosky et al., 2014). Low-dose As exposure also resulted in partially reversible repression of MUC5AC and MUC5B at mRNA and protein levels through retinoic acid signaling pathway (Liu et al., 2020). TGF- β /Smad pathway signaling may be also involved in As-induced fibrosis (Dai et al., 2019).

As exposure was also shown to impair lung epithelial barrier function by causing aberrant localization and expression of tight junction proteins claudin and occludin, as well as impairing occludin

phosphorylation (Sherwood et al., 2013). These data are in agreement with the results of a more recent study demonstrating increased respiratory epithelial permeability and alveolar epithelial type 1 cell injury (Henderson et al., 2017). As-induced decrease in lysozyme secretion was also observed in human bronchial epithelial cells increasing susceptibility to infectious agents (Goodale et al., 2017).

Chowdhury, T., Roymahapatra, G., & Mandal, S. M. (2020). In Silico Identification of a Potent Arsenic Based Approved Drug Darinaparsin against SARS-CoV-2: Inhibitor of RNA dependent RNA polymerase (RdRp) and Necessary Proteases.

1.5.3. Viral diseases, antiviral immunity and immunotoxicity

In contrast to other heavy metals, the role of As in viral diseases is dual. On the one hand, chronic As exposure is known to be tightly associated with the incidence of viral infections due to its immunotoxic effect, whereas on the other, As compounds are used as the potential antiviral agent also inhibiting SARS-CoV-2 viral proteins as assessed by *in silico* docking analysis (Chowdhury et al., 2020). At the same time, arsenic exposure was shown to be associated with increased H1N1 influenza virus load, as well as reduction in FEV1 in a primarily adult population (Liao et al., 2011). In turn, the relationship between As body burden and non-airborne hepatitis A (Cardenas et al., 2016), B (Cardenas et al., 2018; Zhang et al., 2018), and E (Heaney et al., 2015) viral infections may indirectly reflect negative impact of As on antiviral immunity.

It is also notable that As toxicity may underlie impaired antiviral response in the organism (Fig. 3). Particularly, it has been demonstrated that urinary As levels were found to be inversely associated with post-immunization mumps-specific IgG levels (Raqib et al., 2017).

Experimental data corroborate clinical findings. For example, in chicks, As exposure significantly increased susceptibility to Newcastle disease virus resulting in higher virus titers and impaired antibody responses to T-dependent antigen (Sattar et al., 2016). These data generally are in agreement with the earlier observation of impaired antiviral response and higher pulmonary virus titer in a model of H1N1 influenza infection in C57BL/6J mice (Kozul et al., 2009). Moreover, chronic arsenite exposure significantly increased susceptibility to H1N1 influenza infection through sialic acid binding as well as decreased efficiency of oseltamivir (Amouzougan et al., 2020). In addition, prenatal As exposure significantly aggravated influenza A-induced pulmonary inflammation (Ramsey et al., 2013).

An interesting study by Benyamin et al. (2006) demonstrated that coxsackievirus B3 infection in Balb/c mice results in reduced serum, liver, spleen, heart, pancreas, and kidney As levels along with clinical manifestation of the disease (Benyamin et al., 2006).

Nonetheless, several studies demonstrate potential antiviral activity of As compounds. Particularly, As₂O₃ exposure significantly inhibits growth of human T-cell leukemia virus-infected T-cell lines through induction of apoptosis and cell cycle arrest (Ishitsuka et al., 2000). Similarly, As administration was also shown to inhibit Epstein-Barr Virus replication and stimulates cell death in EBV-positive cells (Yin et al., 2017). Due to the observed effects of As exposure on viral agents of leukemia, As and IFN- α is widely used as an antileukemic agent (Hachiman et al., 2018). At the same time, As₂O₃ was also shown to reduce susceptibility to Simian immunodeficiency virus after provirus reactivation in macaques (Yang et al., 2019b). Earlier studies have also demonstrated an inhibitory effect of As₂O₃ on HCV replication (Hwang et al., 2004). Moreover, the results of *in silico* docking analysis demonstrated that certain arsenicals were capable of inhibiting SARS-CoV-2 RNA dependent RNA polymerase thus decreasing viral replication (Chowdhury et al., 2020), although *in vitro* and *in vivo* data are highly required to support this hypothesis.

Generally, the observed difference in As activity is expected to be related to the mode of exposure, where long-term As exposure affects immunity and increases susceptibility to viral agents, whereas acute arsenic exposure may possess antiviral effect due to cytotoxic effect on

virus-infected cell.

Among its adverse outcomes, epidemiological, *in vitro* and *in vivo* evidences indicate that arsenic is an immunotoxic compound, acting as both immune system suppressor and stimulator mechanisms (Ferrario et al., 2016). As was shown to impair proliferation, differentiation, and activation of macrophages, dendritic cells, and T-cells (Bellamri et al., 2018), especially T regulatory cells (Haque et al., 2017). Particularly, male BALB/c mice exposed to 0.038, 0.38 and 3.8 ppm sodium arsenite for 7, 15 and 30 days through oral gavage showed a significant dose-dependent increase in the ThPOK expression levels in thymus, suggesting an impairment in the regulation of CD4⁺ T cells differentiation. In the spleen, As increased the number of CD4⁺ T cells and promoted their differentiation into Treg cells, however, a low secretion of IFN-γ, TNF-α, IL-12, IL-4, IL-5 and IL-10 cytokines was observed in splenocytes (Gera et al., 2017). Activation of NF-κB and downstream signaling was shown to induce As-associated immune suppression (Choudhury et al., 2016).

As₂O₃ exposure resulted in a significant Nrf2-independent inhibition of both mRNA and protein production of IFNγ, IL-2, and GM-CSF in splenocytes (VanDenBerg et al., 2017). It has been also demonstrated that As₂O₃ inhibited IFN-α secretion in plasmacytoid dendritic cells (Ye et al., 2020).

Moreover, another study with lymphocytes isolated from the blood of healthy people, showed that exposure to As at a concentration range of 0.05–50 μM for 12 h was able to induce apoptosis mainly through enhancement of intracellular calcium import which causes oxidative stress. Moreover, cellular proteolysis, activation of caspase-3 and lipid peroxidation with 2, 4 or 6 h of exposure, and stimulation of cytokines (IL-2, INF-γ and TNF- α) production after an exposure of 24 h was also associated with As-induced toxicity in the isolated lymphocytes (Zarei et al., 2019). Overall, these findings indicate that ROS generation followed by inflammation play a crucial role in the cytotoxicity. The alteration of cytokine levels found after As exposure can reflect a commitment of lymphocytes, which in turn impairs immune system in fighting against infection (Zarei et al., 2019). In parallel with impaired lymphocyte functioning, As toxicity is also associated with chronic inflammation and reduced phagocytic receptors—Fcγ and complement receptors (CR) (Prasad, Sinha, 2017). Correspondingly, As exposure was shown to affect innate immunity factors in children (Parvez et al., 2019).

1.6. Toxic metals in internal risk factors for COVID-19 severity

In parallel with respiratory dysfunction, certain diseases are also considered as the most significant co-morbidity risk factors for COVID-19 severity, including obesity, diabetes, cardiovascular diseases (hypertension), and cancer. These diseases may also provide an additional link between COVID-19 severity and heavy metal toxicity. Earlier data demonstrate that obesity and diabetes may be associated with Hg (Tinkov et al., 2015; Roy et al., 2017), Cd (Satarug et al., 2010; Tinkov et al., 2017), Pb (Park et al., 2017; Leff et al., 2017), and As (Farkhondeh et al., 2019). Although these associations are rather contradictory and the underlying mechanisms are still unclear, it is proposed that the role of metals and endocrine disruptors may significantly contribute to metabolic disorders. Heavy metal pollution was also demonstrated to be significantly associated with cardiovascular morbidity predominantly through interference with atherosclerosis (Solenkova et al., 2014). Particularly, Cd (Tellez-Plaza et al., 2013; Tinkov et al., 2018a), Hg (Houston, 2011; Genchi et al., 2017), Pb (Poręba et al., 2011; Xu et al., 2017), and As (Moon et al., 2017; Navas-Acien et al., 2019) exposure levels were directly associated with prevalence of a wide range of cardiovascular diseases including atherosclerosis, coronary heart disease, hypertension, myocardial infarction, stroke, etc. Finally, As and Cd are considered as Group I carcinogens by International Agency for Research on Cancer (IARC).

Table 1

A brief summary of the effects of cadmium, mercury, lead, and arsenic on lung dysfunction, mechanisms of lung toxicity, and immunopathology.

Variable	Patterns	References
Cadmium (Cd)		
Respiratory function	↓ FEV1 (current and former smokers) ↓ FEV1, FVC (children) ↓ FVC, FEV1, FEV1/FVC, PEF (welders)	Mannino et al., 2004 Zeng et al., 2017 Cetintep et al., 2019; Torén et al., 2019
Respiratory diseases	Chronic obstructive pulmonary disease Wheezing	Oh et al., 2014; Sundblad et al., 2016 Razi et al., 2012; Yang et al., 2019a
Lung toxicity mechanisms	Endoplasmic reticulum stress Apoptosis Fibrosis ↓ impaired mucociliary clearance ↓ barrier function and tight junction proteins	Kim et al., 2017 Heo et al., 2017a, 2017b Kiran Kumar et al., 2016 Li et al., 2019 Li et al., 2017a, 2017b Hu et al., 2017 Kim et al., 2018 Xiong et al., 2019 Cao et al., 2015
Respiratory viral infections	Respiratory syncytial virus (mice) H1N1 infection (mice) influenza (MCDK cells)	Go et al., 2018 Chandler et al., 2019 Checconi et al., 2013
Immune cell effects	↓ T-helper (CD4+); ↑ cytotoxic T cells (CD8+) (mice) ↓ splenic NK-cells; ↓ granulocytes (mice) ↑ increased CD4+; CD8+ T cells; CD45R/B220+ B cells (mice) ↓ T lymphocyte (children) ↓ memory T cell (children)	Pathak, Khandelwal, 2008 Holásková et al., 2012 Holásková et al., 2012 Zeng et al., 2020 Nygaard et al., 2017
Cytokine response	↓ IFN-γ; IL-2 (mice) ↑ IFN-γ; IL-10 (rats) (activated T cells) ↑ TNF-α; Nrf2; NF-κB (zebrafish) ↓ IL-6; IL-10; IL-1β; TNF-α (zebrafish) ↑ IL-1β; CXCL1; ↓ IL-6; IL-10 (RAW 264.7 macrophages)	Pathak, Khandelwal, 2008 Turley et al. 2019 Zheng et al. 2016 Guo et al. 2017 Riemenschneider et al. 2015
Mercury (Hg)		
Respiratory function	↓ FVC, FEV1 (artisanal and small-scale gold mining area)	Pateda et al., 2018
Respiratory diseases	COPD (dusty area) Asthma and bronchi hyperresponsiveness (children) Recurrent wheezing (children) Lower respiratory infections (infants)	Heo et al., 2017a, 2017b Kim et al., 2015 Razi et al., 2011 Emeny et al., 2019
Lung toxicity mechanisms	Oxidative stress Apoptosis Endoplasmic reticulum stress Inflammation	Yu et al., 2015; Park, Park, 2007; Han et al., 2007 Yu et al., 2015; Park, Park, 2007; Ali et al., 2018; Lu et al., 2010 Jagannathan et al., 2017 Liu et al., 2003 Naidoo et al., 2019
Respiratory viral infections	Measles (children) Rubeola (children) Coxsackievirus b3 (mice) Coxsackievirus b3 (mice)	Gallagher et al., 2011 Gallagher et al., 2013 Nyland et al., 2012; Penta et al., 2015b Ilbäck et al., 2005 Ilbäck et al., 2008
Immune cell effects	↓ T cell (Jurkat cell line) ↑ T cell and ↓ B cell proliferation (Steller sea lion)	Guzzi et al., 2012 Levin et al., 2020

(continued on next page)

Table 1 (continued)

Variable	Patterns	References
	↓ CD3+CD4+; Th1; Th17 cells (mice)	Batista-Duharte et al., 2018
Cytokine response	↓ INF-γ, IL-6, IL-10, and TNF-α (Steller sea lion) ↓ interferon-γ (IFN-γ) ↑ TNF-α -related gene expression (mice) ↑ NF-κB (C17.2 cells)	Levin et al., 2020 De Vos et al., 2007 Iwai-Shimada et al. 2016 Iwai-Shimada et al. 2016
Lead (Pb) Respiratory function	↓ VC; FVC Polish schoolchildren FEV1 children e-waste emission area FEV1 FEV1 and FVC	Little et al., 2017 Zeng et al., 2017 Wei et al., 2020 Pan et al., 2020
Respiratory diseases	COPD Total	Gogoi et al., 2019 Ghias, Mohammadzadeh, 2016
Lung toxicity mechanisms	Oxidative stress Inflammation Fibrosis Apoptosis Mitochondrial dysfunction	Lu et al., 2015 Kaczyńska et al., 2011; Li et al., 2013; Attafi et al., 2018 Kaczyńska et al., 2013; Attafi et al., 2018 Alarifi et al., 2017; Lu et al., 2018; Ahmed et al., 2019 Alarifi et al., 2017
Respiratory viral infections	-	-
Immune cell effects	↓ lymphocyte proliferation (mice) ↓ T cell (Pb-exposed subjects) Altered Th1/Th2 ratio (chicken) ↑ memory T cells (children, e-waste-recycling area)	Li et al., 2012 Mishra et al., 2010 Fu et al., 2019 Cao et al., 2018
Cytokine response	↓ IFN-γ (Macrophage and B-cell lines) ↑ NF-κB, AhR (A549 lung cells) ↑ IL-1β, 1R, 4, 8, 10, 12β; ↓IL-2, IFN-γ (chicken) ↓ IL-2, IFN-γ, IL-4, IL-10, TNF-α (mice) ↑ IL-5, IL-10; ↓TNF-α, IFN-γ (mice)	Han et al., 2020 Attafi et al., 2020 Xing et al., 2018 Ajouaoi et al., 2019 Dvoroznáková et al., 2016
Arsenic (As) Respiratory function	↓ FEV1, FVC (meta-analysis) ↓ FVC (early life exposed subjects) ↓ FVC; ↑ cough, shortness of breath (adults, Northern Chile) ↓ FEV1, FVC (As-exposed children) ↓ FEV1, FEV1/FVC, FEF75 (coal-burning areas)	Sanchez et al., 2018 Khan et al., 2020 Nardone et al., 2017 Olivas-Calderón et al., 2015; Ahmed et al., 2017 Wang et al., 2020
Respiratory diseases	Chronic bronchitis Reversible lung obstruction Lower respiratory tract infections Pneumonia	Steinmaus et al., 2016; Powers et al., 2018 Siddique et al., 2020 Farzan et al., 2013 George et al., 2015
Lung toxicity mechanisms	Inflammation Altered lung morphogenesis, ciliary function Fibrosis Altered barrier function and tight junction proteins Impaired respiratory epithelial permeability	Surolia et al., 2020; Zhao et al., 2019; Hu et al., 2019 Zosky et al., 2014 Dai et al., 2019 Sherwood et al., 2013 Henderson et al., 2017
	H1N1 influenza (adults)	Liao et al., 2011 Sattar et al., 2016

Table 1 (continued)

Variable	Patterns	References
Respiratory viral infections	Newcastle disease virus (chicks) H1N1 influenza (mice)	Kozul et al., 2009; Amouzougan et al., 2020
	Influenza A (mice) Coxsackievirus B3 (mice)	Ramsey et al., 2013 Benyamin et al., 2006
Immune cell effects	↓ human T-cell growth ↓ macrophages, dendritic cells, and T-cells ↓ T regulatory cells ↑ CD4+ T cells and Treg differentiation	Ishitsuka et al., 2000 Bellamri et al., 2018 Haque et al., 2017 Gera et al. 2017
Cytokine response	↓ IFN-γ, TNF-α, IL-12, IL-4, IL-5 and IL-10 (splenocytes mice) ↑ NF-κB, MAPK	Gera et al. 2017 Choudhury et al., 2016; Li et al., 2017a, 2017b; Hu et al., 2019
	↓ IFN-γ, IL-2, GM-CSF (splenocytes mice) ↓ IFN-α (plasmacytoid dendritic cells) ↑ IL-2, INF-γ, TNF-α (human lymphocytes)	VanDenBerg et al., 2017 Ye et al., 2020 Zarei et al. 2019

AhR - Aryl hydrocarbon receptor; COPD - Chronic obstructive pulmonary disease; CXCL1 - chemokine (C-X-C motif) ligand 1; FEF75 - forced expiratory flow at 75% of FVC; FEV1 - Forced Expiratory Volume in one second; FVC - Forced Vital Capacity; IFN-γ - interferon-γ; IL - interleukin; MAPK - Mitogen-activated protein kinase; NF-κB - nuclear factor κB; Nrf2 - Nuclear factor erythroid 2-related factor 2; PEF - Peak expiratory flow; TNF-α - Tumor necrosis factor-α; VC - vital capacity

2. Conclusion

Taken together, the existing data demonstrate that As, Cd, Hg, and Pb exposure is associated with respiratory dysfunction (reduced FVC, FEV1) and respiratory diseases (COPD, bronchitis). These observations corroborate laboratory findings on the role of heavy metal exposure in impaired mucociliary clearance, reduced barrier function, airway inflammation, oxidative stress, and apoptosis. Both clinical and laboratory studies have shown the association between heavy metal exposure and severity of viral diseases, including influenza and respiratory syncytial virus. The latter may be considered a consequence of adverse effects of metal exposure on adaptive immunity (Table 1).

Although direct data linking heavy metal exposure and COVID-19 risk and/or severity are lacking, reduction in heavy metal emissions may significantly reduce lung immunopathology and inflammation, both of which are known to increase the risk of respiratory viral and bacterial diseases. In addition, avoiding heavy metal exposure at the individual level through the use of respirator masks or portable air filters, especially in highly-polluted environments including metropoles, could also contribute to reduction of risk of infection and its severity. The use of zinc, selenium, or other functional antagonists of heavy metals may also prevent adverse effects of heavy metals on respiratory system and immunity. At the same time, both epidemiological and laboratory studies are urgently required to characterize the direct association between heavy metal exposure and COVID-19 risk and pathogenetic mechanisms.

CRedit authorship contribution statement

Anatoly V. Skalny: Supervision, Conceptualization. **Thania Rios Rossi Lima:** Writing - original draft, Data curation, Formal analysis, Investigation, Visualization. **Tao Ke:** Writing - original draft, Data curation, Formal analysis, Formal analysis, Investigation, Investigation. **Ji-Chang Zhou:** Writing - original draft, Data curation. **Julia Bornhorst:** Writing - original draft, Data curation, Formal analysis,

Investigation, Visualization. Svetlana I. Alekseenko: Writing - original draft, Data curation, Formal analysis, Investigation. Jan Aaseth: Writing - review & editing, Supervision, Conceptualization. Ourania Anesti: Writing - original draft, Data curation, Formal analysis, Investigation. Dimosthenis A. Sarigiannis: Writing - original draft, Data curation, Formal analysis, Investigation. Aristides Tsatsakis: Writing - review & editing, Supervision, Conceptualization. Michael Aschner: Writing - review & editing, Supervision, Conceptualization. Alexey A. Tinkov: Writing - review & editing, Writing - original draft, Data curation, Formal analysis, Investigation, Conceptualization, Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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